receptor protein for a time sufficient for said detectable oligonucleotide probes to hybridize to mRNA that encodes ST receptor protein present in cells of said sample;

b) removing detectable oligonucleotide probes which are not hybridized to mRNA that encodes ST receptor protein in cells of said sample; and

c) examining said sample to detect the presence of detectable oligonucleotide probes hybridized to mRNA that encodes ST receptor protein present in cells in the basement membrane of the laminapropria;

wherein the presence of mRNA that encodes ST receptor protein in cells in the basement membrane of the laminapropria indicates invasion of neoplastic colorectal cells into the basement membrane of the laminapropria of an individual.

REMARKS

Claims 23 to 26 are pending in the present application and claims 23 and 25 have been amended herein.

I. The Specification Fully Enables Practice of the Claimed Methods

Claims 23 to 26 stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicant respectfully traverses the rejection.

Applicant respectfully submits that the specification enables one of ordinary skill in the art to practice the full scope of the subject matter defined by the present claims without undue experimentation. It is well-settled that the first paragraph of § 112 requires nothing more than

objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance. *In re Marzocchi*, 169 U.S.P.Q. 152 (C.C.P.A. 1975). The Patent Office has the burden of giving reasons, supported by the record as a whole, why the specification is not enabling. *In re Armbruster*, 185 U.S.P.Q. 152 (C.C.P.A. 1975). It is submitted respectfully that this burden has not been met in the present case.

The specification teaches that

> [n]ormal tissue in the body does not have ST receptors or mRNA encoding ST receptors except cells of the intestinal tract. Thus, if non-colorectal samples possess ST receptors metastasis of colorectal tumor cells is indicated. Thus, metastasized colorectal cells may be identified by detecting in non-colorectal samples ST receptors or mRNA encoding ST receptors.

See page 11, lines 5 to 11. The specification further highlights the fact that, utilizing the sequence information provided in *Sauvage et al., J. Biol. Chem.* 266, 1991, 17912-17918, the design of probes that *selectively* hybridize to human mRNA encoding the ST receptor protein is within the expertise of the skilled artisan. *See* page 33, lines 3 to 13. The specification thus teaches the skilled artisan how to design probes that selectively hybridize to human mRNA encoding the ST receptor protein, and further teaches the skilled artisan how to use the probes in *in situ* methods to detect the invasion of neoplastic colorectal cells into the basement membrane of the laminapropria. *See* page 33, line 3 to page 34, line 19. The specification thus enables the full scope of the subject matter defined by the present claims.

The Office Action asserts that "the prior art teaches that while the protein [ST receptor protein] is expressed only in intestinal cells, it is possible to detect encoding mRNA in other cells

by oligonucleotide probe methods." *See* Office Action mailed January 31, 2001, page 5. Applicant submits that the cited references do *not* teach that mRNA may be detected in human cells other than intestinal cells by oligonucleotide probe methods that have comparable sensitivity to that of *in situ* hybridization. Table I of *Schulz, et al.* (*J. Biol. Chem.* 267(3), 1992, 16019-16021) (hereinafter "the Schulz reference") depicts the results of experiments in which Northern analysis was performed using probes comprising the gene encoding rat Guanylyl cyclase C (GC-C) (an ST receptor) and mRNA isolated from various rat, human, and bovine cell types. The probes hybridized to mRNA isolated from human T84 cells (human colonic adenocarcinoma cells isolated from lung metastases) but did not hybridize to mRNA isolated from human airway epithelial cells. The Schulz reference thus teaches that mRNA encoding an ST receptor may be detected by oligonucleotide probe methods in human colonic adenocarcinoma cells and does *not* teach that such mRNA may be detected in other human cell types by oligonucleotide probe methods.

Table I of the Schulz reference also depicts the results of experiments in which the polymerase chain reaction was performed using GC-C specific primers and, in some experiments, degenerate primers, to amplify mRNA isolated from various rat, human and bovine cell types. *See* pages 16019-16020 and page 16021. The reference does not disclose the particular experiments in which degenerate primers were used. Notably, the polymerase chain reaction is far more sensitive than *in situ* hybridization, potentially resulting in the amplification of mRNA that would not be detected by *in situ* hybridization methods. Moreover, degenerate primers were used in some PCR reactions, creating the possibility that mRNA encoding GC-C may not actually have been amplified. The results of the PCR experiments reported in the Schulz reference therefore cannot validly be

compared to the *in situ* methods claimed in the present application and thus are not relevant to determining whether the specification enables the present claims. Applicant respectfully submits that the specification enables the full scope of the subject matter defined by the present claims and accordingly requests withdrawal of the rejection upon reconsideration.

II. Rejection Under 35 U.S.C. § 112, Second Paragraph and Claim Objections

Claims 23 to 26 stand rejected under 35 U.S.C. § 112, second paragraph because the phrase "contacting said tissue" of claim 23 is allegedly vague and indefinite.

Applicant submits that the cited term conveys a clear and definite meaning to the skilled artisan; nevertheless, claim 23 has been amended in order to advance prosecution by replacing the phrase "contacting said tissue" with the phrase "contacting said sample." Support for the amendment is found in the specification at, for example, page 33 line 3 to page 34, line 19. Applicant submits respectfully that the rejection has been obviated by amendment and respectfully requests withdrawal thereof.

Claims 23 and 25 were objected to due to the presence of typographical errors. The errors have been corrected by replacing "laminapropia" with "laminapropria" and by replacing "hybridize" with "hybridized."

III. Alleged Double Patenting

Claims 23 to 26 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims one and four of U.S. Patent

No. 5,601,990. Applicant requests that this rejection be deferred pending some identification of allowable subject matter, as it likely can be readily resolved (depending upon the subject matter ultimately allowed) through the filing of a suitable terminal disclaimer.

IV. Conclusion

In view of the foregoing, Applicant submits that the claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

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Date: July 26, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

23. (Amended) An in situ method of detecting invasion of neoplastic colorectal cells into the basement membrane of the [laminapropia] laminapropria of [an individual] a human comprising the steps of:

a) obtaining a sample of intestinal tissue which includes the basement membrane of the [laminapropia] laminapropria;

b) contacting said [tissue] sample with detectable oligonucleotide probes that hybridize to mRNA that encodes ST receptor protein for a time sufficient for said detectable oligonucleotide probes to hybridize to mRNA that encodes ST receptor protein present in cells of said sample;

c) removing detectable oligonucleotide probes which are not hybridized to mRNA that encodes ST receptor protein in cells of said sample; and

d) examining said sample to detect the presence of detectable oligonucleotide probes [hybridize] hybridized to mRNA that encodes ST receptor protein present in cells in the basement membrane of the [laminapropia] laminapropria;

wherein the presence of mRNA that encodes ST receptor protein in cells in the basement membrane of the [laminapropia] laminapropria indicates invasion of neoplastic colorectal cells into the basement membrane of the [laminapropia] laminapropria of an individual.

25. (Amended) An in situ method of detecting invasion of neoplastic colorectal cells into the basement membrane of the [laminapropia] laminapropria of [an individual] a human comprising the steps of:

a) contacting a sample of intestinal tissue which includes the basement membrane of the [laminapropia] laminapropria with detectable oligonucleotide probes that hybridize to mRNA that encodes ST receptor protein for a time sufficient for said detectable oligonucleotide probes to hybridize to mRNA that encodes ST receptor protein present in cells of said sample;

b) removing detectable oligonucleotide probes which are not hybridized to mRNA that encodes ST receptor protein in cells of said sample; and

c) examining said sample to detect the presence of detectable oligonucleotide probes [hybridize] hybridized to mRNA that encodes ST receptor protein present in cells in the basement membrane of the [laminapropia] laminapropria;

wherein the presence of mRNA that encodes ST receptor protein in cells in the basement membrane of the [laminapropia] laminapropria indicates invasion of neoplastic colorectal cells into the basement membrane of the [laminapropia] laminapropria of an individual.